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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07K 5/062, 5/083, 5/103, 5/078, 5/117,</b> <b>A61K 38/05, 38/06, 38/07</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/22620</b> <b>(43) International Publication Date:</b> 26 June 1997 (26.06.97)
<b>(21) International Application Number:</b> PCT/EP96/05393 <b>(22) International Filing Date:</b> 4 December 1996 (04.12.96)  <b>(30) Priority Data:</b> MI95A002681 20 December 1995 (20.12.95) IT  <b>(71)(72) Applicant and Inventor:</b> DEGHENGHI, Romano [IT/CH]; Cheseaux Dessus B1, CH-1264 St. Cergue (CH).  <b>(74) Agent:</b> SPADARO, Marco; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> OLIGOPEPTIDE COMPOUNDS CONTAINING D-2-ALKYLTRYPTOPHAN CAPABLE OF PROMOTING THE RELEASE OF GROWTH HORMONE  <b>(57) Abstract</b>  A peptide of formula: A-D-X-D-Mrp-B wherein A is hydrogen, 2-aminoisobutyl, 4-aminobutyl, D relates to the dextro isomer, X is Mrp, wherein Mrp means 2-alkyltryptophan or X is a residue of protected serine, Ser (Y), wherein Y can be benzyl, p-chlorobenzyl, 4-methoxybenzyl, 2,4,6-trimethoxybenzyl, tert-butyl; B is NR <sub>2</sub> R <sub>3</sub> , wherein R <sub>2</sub> and R <sub>3</sub> , which can be the same or different, are hydrogen or a C <sub>1</sub> -C <sub>3</sub> alkyl group; an OR <sub>4</sub> group, wherein R <sub>4</sub> is hydrogen or a C <sub>1</sub> -C <sub>3</sub> alkyl C-Lys-NH <sub>2</sub> group, wherein C is Phe or Mrp, and the addition salts with pharmaceutically acceptable organic or inorganic acids of anyone of said polipeptides; these compounds are capable of promoting the release of growth hormone and they are active by the oral route.		

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OLIGOPEPTIDE COMPOUNDS CONTAINING D-2-ALKYLTRYPTOPHAN  
CAPABLE OF PROMOTING THE RELEASE OF GROWTH HORMONE

The present invention relates to oligopeptide compounds containing a D-2-alkyltryptophan amino acid and having and which are capable of releasing growth hormone (GH) from somatotropes, and are active by oral  
5 route.

Background of the invention

The increase of growth hormone (GH) levels in mammals after the administration of compounds inducing GH release can yield to growth acceleration and muscular  
10 mass increase and enhanced production of milk, if sufficiently high GH levels are obtained after the administration. Moreover, it is known that the increase of growth hormone levels in mammals can be achieved by administering known growth hormone release agents, such  
15 as growth hormone release hormones (GHRH).

The increase of growth hormone levels in mammals can also be obtained by administering growth hormone release peptides, some of them having previously been described, for example in US 4,223,019, US 4,223,020, US  
20 4,223,021, US 4,224,316, US 4,226,857, US 4,228,155, US 4,228,156, US 4,228,157, US 4,228,158, US 4,410,512, US 4,410,513, US 4,411,890 and US 4,839,344.

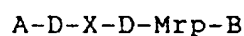
Therefore, rather simple short chain-oligopeptides, capable of promoting growth hormone release on condition  
25 that they are easily and conveniently preparable, as well as of easy purification and formulation and active when administered by the oral route, are presently desired.

Summary of the invention

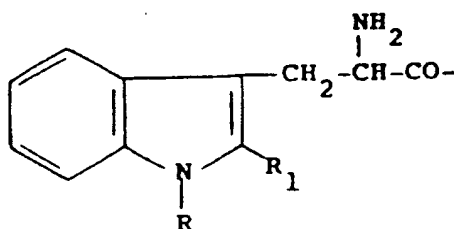
In a completely surprising manner it has now been found that very short oligopeptides, having at least one D-2-alkyltryptophan (2-Mrp) residue, have activity  
 5 releasing growth hormone (GH) from somatotropes.

Another unexpected distinctive feature of the present invention is the very high potency and the favourable oral activity oral/potency ratio that even the smallest tripeptides of the series exhibit.

10 The oligopeptides of the present invention have the formula:



wherein A is hydrogen, 2-aminoisobutyl, 4-aminobutyl, D relates to the dextro isomer, X is Mrp,  
 15 wherein Mrp means 2-alkyltryptophan of formula:



20

wherein R is hydrogen, CHO, SO<sub>2</sub>CH<sub>3</sub>, mesitylene-2-sulfonyl, PO<sub>3</sub>(CH<sub>3</sub>)<sub>2</sub>, PO<sub>3</sub>H<sub>2</sub>; R<sub>1</sub> is a C<sub>1</sub>-C<sub>3</sub> alkyl group;  
 or

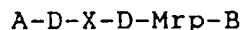
X is a residue of protected serine, Ser (Y), wherein Y  
 25 can be benzyl, p-chlorobenzyl, 4-methoxybenzyl, 2,4,6-trimethoxybenzyl, tert-butyl; B is NR<sub>2</sub>R<sub>3</sub>, wherein R<sub>2</sub> e R<sub>3</sub>, which can be the same or different, are hydrogen or a C<sub>1</sub>-C<sub>3</sub> alkyl group; a OR<sub>4</sub> group, wherein R<sub>4</sub> is hydrogen or a C<sub>1</sub>-C<sub>3</sub> alkyl C-Lys-NH<sub>2</sub> group, wherein C is Phe or

Mrp.

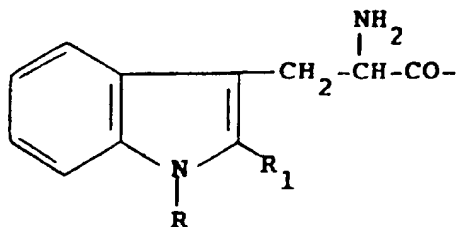
# Detailed Disclosure of the Invention

The present invention lies on the discovery that different short-chain oligopeptides which promote the release and increase of growth hormone levels in blood of animals are characterized in that all of them comprise in the peptide chain a D-isomer of 2-alkyltryptophan (D-2-Me-Trp or D-Mrp).

The oligopeptides comprised in the scope of the present invention are defined by the following formula



wherein A is hydrogen, 2-aminoisobutyryl, 4-aminobutyryl, D relates to the dextro isomer, X is Mrp, wherein Mrp means 2-alkyltryptophan of formula:



wherein R is hydrogen, CHO, SO<sub>2</sub>CH<sub>3</sub>, mesitylene-2-sulfonyl, PO<sub>3</sub>(CH<sub>3</sub>)<sub>2</sub>, PO<sub>3</sub>H<sub>2</sub>; R<sub>1</sub> is a C<sub>1</sub>-C<sub>3</sub> alkyl group; or

X is a residue of protected serine, Ser (Y), wherein Y can be benzyl, p-chlorobenzyl, 4-methoxybenzyl, 2,4,6-trimethoxybenzyl, tert-butyl; B is NR<sub>2</sub>R<sub>3</sub>, wherein R<sub>2</sub> and R<sub>3</sub>, which can be the same or different, are hydrogen or a C<sub>1</sub>-C<sub>3</sub> alkyl group; a OR<sub>4</sub> group, wherein R<sub>4</sub> is hydrogen or a C<sub>1</sub>-C<sub>3</sub> alkyl C-Lys-NH<sub>2</sub> group, wherein C is Phe or Mrp, and the addition salts with pharmaceutically

acceptable organic or inorganic acids of any one of said polipeptides.

The abbreviations for the residues of amino acids herein used are in agreement with the standard nomenclature for the peptides:

Lys = L-Lysine.

Moreover,

Aib = 2-aminoisobutyryl;

GAB = 4-aminobutyryl;

10 Mrp = 2-alkyltryptophan;

Bzl = benzyl;

p-Cl-Bzl = p-chlorobenzyl;

Mob = 4-methoxybenzyl;

Tmob = 2,4,6-trimethoxybenzyl;

15 tbu = tert-butyl;

For = formyl;

Mts = mesitylene-2-sulfonyl.

According to the present invention, alkyl means lower alkyl, comprising from 1 to 3 carbon atoms. Examples of lower alkyl are methyl, ethyl, propyl, isopropyl. Among these, the methyl group is most preferred.

All the three letter-abbreviations of the amino acids preceded by a "D" indicate the D-configuration of the amino acid residue. When the amino acid is referred to with the only three-letter abbreviation, it has L configuration.

The preferred growth hormone-release compounds of the present invention are:

30 (a) GAB-D-Mrp-D-Mrp-Phe-Lys-NH<sub>2</sub>;

(b) GAB-D-Mrp-D-Mrp-Mrp-Lys-NH<sub>2</sub>;

5

(c) Aib-D-Mrp-D-Mrp-NH<sub>2</sub>;

(d) Aib-D-Mrp-Mrp-NH<sub>2</sub>;

(e) Aib-D-Ser(Bzl)-D-Mrp-NH<sub>2</sub>;

wherein Mrp is 2-methyltryptophan, GAB and Aib are as  
5 defined above, and the addition salts with  
pharmaceutically acceptable organic or inorganic acids  
of anyone of said oligopeptides.

These compounds are preferably administered by the  
oral route, but they also can be administered  
10 intranasally or parenterally, or they can be formulated  
in controlled release systems, such as biodegradable  
microcapsules, microspheres, subcutaneous implants and  
the like.

The oligopeptide compounds according to the present  
15 invention can be synthesized according to the usual  
methods of peptide chemistry, both solid-phase and  
solution, or by means of the classical methods known in  
the art. The solid-phase synthesis starts from C-  
terminal end of peptide. A suitable starting material  
20 can be prepared, for example attaching the required  
protected alpha-amino acid to a chloromethylated resin,  
a hydroxymethylated resin, a benzhydrylamine resin  
(BHA), or to a para-methylbenzhydrylamine resin (p-Me-  
BHA). As example, a chloromethylated resin is sold with  
25 the Trade Mark BIOBEADS (R) SX 1 by BioRad Laboratories,  
Richmond, California. The preparation of the  
hydroxymethyl resin is described by Bodansky et al.,  
Chem. Ind. (London) 38, 15997, (1966). The BHA resin is  
described by Pietta and Marshall, Chem. Comm., 650  
30 (1970), and is commercially available by Peninsula  
Laboratories Inc., Belmont, California.

After the starting attachment, the alpha-amino acid-protecting group can be removed by means of different acid reagents, comprising trifluoroacetic acid (TFA) or hydrochloric acid (HCl) dissolved in organic solvents at room temperature. After the removal of the alpha-amino acid-protecting group, the remaining protected amino acids can be coupled step by step in the desired order. Each protected amino acid can generally be reacted in excess of about three times using a suitable carboxyl activating group, such as dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide (DIC) dissolved, for example, in methylene chloride ( $\text{CH}_2\text{Cl}_2$ ) or dimethylformamide (DMF) and their mixtures. After the desired amino acid sequence has been completed, the desired peptide can be cleaved from the supporting resin by treatment with a reagent such as hydrogen fluoride (HF), which not only cleaves the peptide from the resin, but also the more common protecting groups of the lateral chains. When a chloromethylated resin or a hydroxymethylated resin is used, the treatment with HF leads to the formation of the acid peptide in free form. When a BHA or p-Me-BHA resin is used, the treatment with HF directly leads to the formation of the amide peptide in free form.

The above discussed solid-phase procedure is known in the art and was described by Atherton and Sheppard, Solid Phase Peptide Synthesis (IRL Press, Oxford, 1989).

Some methods in solution, which can be used to synthesize the peptide moieties of the present invention are detailed in Bodansky et al., Peptide Synthesis, 2<sup>nd</sup> edition, John Wiley & Sons, New York, N.Y. 1976 and from



Jones, The Chemical Synthesis of Peptides, (Clarendon Press, Oxford, 1994).

These compounds can be administered to animals and humans at an effective dose which can be easily  
5 determined by the expert in the field and which can vary according to the specie, age, sex and weight of the treated subject. For example, in humans, when intravenously administered, the preferred dose falls in the range from about 0.1 µg to 10 µg of total peptide  
10 per kg of body weight. When orally administered, typically higher amounts are necessary. For example, in humans for the oral administration, the dosage level is typically from about 30 µg to about 1000 µg of polypeptide per kg of body weight. The exact level can  
15 be easily determined empirically based on the above disclosure.

Compositions, which comprise as active ingredient the organic and inorganic addition salts of the above described oligopeptides and their combinations,  
20 optionally, in admixture with a vehicle, diluent, matrix or delayed release coating, are also comprised in the scope of the present invention. The delayed release pharmaceutical forms, comprising bioerodible matrixes, suitable for subcutaneous implant are particularly  
25 interesting. Examples of these matrices are described in WO9222600 and WO9512629.

#### Biological activity

In vivo activity of these compounds was determined in ten day-rats, which were subcutaneously injected  
30 (s.c.), with a dose of 300 µg/kg or with different doses in dose-response studies, according to what described in

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detail by R. Deghenghi et. al, Life Sciences 54, 1321, (1994). The results are resumed in the Table below, the released GH was measured after 15 minutes from the treatment.

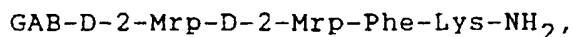
5 TABLE

	Peptide of example	Dose µg/kg s.c.	released GH (ng/ml)
10	1	300	155.4 ± 19.7
	2	300	165.4 ± 18.5
	3	300	174.2 ± 25.9
	4	300	64.2 ± 12.6
	5	1.2 mg/kg	59.4 ± 12.3
15	Controls	-	7 - 23

The following examples further illustrate the invention:

Example 1

20 Making use of the solid-phase peptide synthesis technique as described in "Solid phase peptide synthesis" by E.Atherton and R.C. Sheppard, IRL Press, Oxford University Press, 1984, using fluorenylmethoxycarbonyl (Fmoc) as the protecting group,  
25 the peptide:



was prepared, wherein Mrp is 2-methyltryptophan, M.W. 779.9, found 778.4; purity (HPLC) 98.0%.

Example 2

30 Analogously to Example 1, the following peptide was prepared:

GAB-D-2-Mrp-D-2-Mrp-2-Mrp-Lys-NH<sub>2</sub>,

wherein Mrp is 2-methyltryptophan, M.W. 830.8, found 831.3; purity (HPLC) 98.0%.

Example 3

5 Analogously to Example 1, the following peptide was prepared:

Aib-D-2-Mrp-D-2-Mrp-NH<sub>2</sub>,

wherein Mrp is 2-methyltryptophan, M.W. 502.6, found 503.3; purity (HPLC) 99.0%.

10 Example 4

Analogously to Example 1, the following peptide was prepared:

Aib-D-2-Mrp-2-Mrp-NH<sub>2</sub>.

15 wherein Mrp is 2-methyltryptophan, M.W. 502.6, found 503.3; purity (HPLC) 99.0%.

Example 5

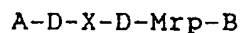
Analogously to Example 1, the following peptide was prepared:

Aib-D-Ser(Bzl)-D-Mrp-NH<sub>2</sub>.

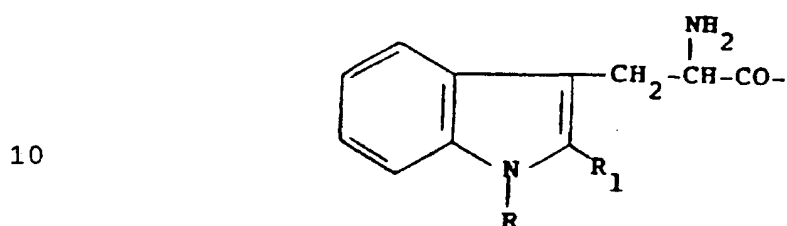
20 wherein Mrp is 2-methyltryptophan, M.W. 479.6, found 480.5; purity (HPLC) 99.0%.

CLAIMS

1. A peptide of formula:



5 wherein A is hydrogen, 2-aminoisobutyryl, 4-aminobutyryl, D relates to dextro isomer, X is Mrp, wherein Mrp means 2-alkyltryptophan of formula:



wherein R is hydrogen, CHO, SO<sub>2</sub>CH<sub>3</sub>, mesitylene-2-sulfonyl, PO<sub>3</sub>(CH<sub>3</sub>)<sub>2</sub>, PO<sub>3</sub>H<sub>2</sub>; R<sub>1</sub> is a C<sub>1</sub>-C<sub>3</sub> alkyl group; or

15 X is a residue of protected serine, Ser (Y), wherein Y can be benzyl, p-chlorobenzyl, 4-methoxybenzyl, 2,4,6-trimethoxybenzyl, tert-butyl; B is NR<sub>2</sub>R<sub>3</sub>, wherein R<sub>2</sub> e R<sub>3</sub>, which can be the same or different, are hydrogen or a C<sub>1</sub>-C<sub>3</sub> alkyl group; a OR<sub>4</sub> group, wherein R<sub>4</sub> is hydrogen or a C<sub>1</sub>-C<sub>3</sub> alkyl C-Lys-NH<sub>2</sub> group, wherein C is Phe or  
20 Mrp,

and the addition salts with pharmaceutically acceptable organic or inorganic acids of anyone of said polipeptides.

25 2. The peptide according to claim 1, wherein Mrp is selected from 2-methyltryptophan, 2-ethyltryptophan, 2-propyltryptophan, 2-isopropyltryptophan.

3. A peptide according to claim 1, wherein Mrp is 2-methyltryptophan.

30 4. The peptide according to claim 1, wherein A is 2-

11

aminoisobutyryl, 4-aminobutyryl.

5. The peptide according to claim 1, wherein B is C-LysNH<sub>2</sub> wherein C is as defined above.

6. The peptide according to claim 1, having formula:

5 GAB-D-Mrp-D-Mrp-Phe-Lys-NH<sub>2</sub>.

7. The peptide according to claim 1, having formula:

GAB-D-Mrp-D-Mrp-Mrp-Lys-NH<sub>2</sub>.

8. The peptide according to claim 1, having formula:

Aib-D-Mrp-D-Mrp-NH<sub>2</sub>.

10 9. The peptide according to claim 1, having formula:

Aib-D-Mrp-Mrp-NH<sub>2</sub>.

10. The peptide according to claim 1, having formula:

Aib-D-Ser(Bzl)-D-Mrp-NH<sub>2</sub>.

11. A peptide according to claims 6-10, wherein Mrp is

15 2-methyltryptophan.

12. The use of the peptides of claims 1-11 for the manufacturing of a medicament useful for promoting the release of growth hormone in an animal.

13. The use according to claim 12, wherein the medicament is useful in human medicine.

14. Pharmaceutical compositions comprising an effective amount of at least one peptide of claims 1-11 as active ingredient, optionally in admixture with carriers and excipients.

25 15. Pharmaceutical compositions according to claim 14 in the form of compositions for parenteral, intranasal, oral, controlled release administrations, subcutaneous implants.

16. Compositions according to claim 14 in the form of  
30 compositions for the oral administration.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 96/05393

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K5/062 C07K5/083 C07K5/103 C07K5/078 C07K5/117  
A61K38/05 A61K38/06 A61K38/07

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 96 10040 A (DEGHENGI, ROMANO, ST. CERGUE, CH) 4 April 1996 Table and Claims ---	1-16
Y	J. PEDIATRIC ENDOCRIN. & METABOL., vol. 8, 1995, pages 311-313, XP000651785 DEGHENGI R. ET AL.: "Small Peptides as Potent Releasers of Growth Hormone" whole Document, especially Table ---	1-16
Y	WO 91 18016 A (DEGHENGI ROMANO, ST. CERGUE, CH) 28 November 1991 whole Document, especially claim 1 and pages 5-6 --- -/--	1-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

13 March 1997

Date of mailing of the international search report

11.04.97

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# INTERNATIONAL SEARCH REPORT

Int. l. Application No  
PCT/EP 96/05393

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LIFE SCIENCES, vol. 54, no. 18, 1994, pages 1321-1328, XP000651534 DEHENGHI R. ET AL.: "GH-REleasing Activity of Hexarelin, a new Growth Hormone Releasing Peptide, in Infant and Rats " page 1323 ---	1-16
A	EP 0 018 072 A (BECKMANN INSTRUMENTS INC. FULLERTON CALIFORNIA, US) 29 October 1980 whole document -----	1-16

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/05393

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9610040 A	04-04-96	IT M1951293 A AU 3566895 A ZA 9507977 A	16-12-96 19-04-96 15-03-96
WO 9118016 A	28-11-91	IT 1240643 B AT 114321 T AU 657475 B AU 7699791 A CA 2081450 A DE 69105270 D DE 69105270 T EP 0531461 A ES 2067256 T	17-12-93 15-12-94 16-03-95 10-12-91 12-11-91 05-01-95 13-04-95 17-03-93 16-03-95
EP 18072 A	29-10-80	US 4223019 A US 4228156 A US 4228157 A US 4228155 A US 4224316 A US 4226857 A US 4228158 A US 4223020 A US 4223021 A AU 5680180 A CA 1175810 A JP 1513250 C JP 61289098 A JP 63060039 B JP 1385850 C JP 55133344 A JP 61046000 B JP 1049359 B JP 1566147 C JP 59216860 A	16-09-80 14-10-80 14-10-80 14-10-80 23-09-80 07-10-80 14-10-80 16-09-80 16-09-80 02-10-80 09-10-84 24-08-89 19-12-86 22-11-88 26-06-87 17-10-80 11-10-86 24-10-89 25-06-90 06-12-84